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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/779,543	WILLIAMS ET AL.	
	Examiner	Art Unit	
	Angela M. Bertagna	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 June 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7,9,11-13,30-32 and 34-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7,9,11-13,30-32 and 34-37* is/are rejected.

7)☒ Claim(s) *9* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. Applicant's response filed on June 23, 2009 is acknowledged. Claims 7, 9, 11-13, 30-32, and 34-37 are currently pending. In the response, Applicant amended claims 9, 30, and 34 and added claims 36 and 37.

Applicant's amendments to claims 9, 30, and 34 have overcome the previously made objections, and therefore, they have been withdrawn.

The following include new grounds of rejection necessitated by Applicant's amendment (see section 4).

Applicant's arguments filed on June 23, 2009 have been fully considered, but they were not persuasive for the reasons set forth in the "Response to Arguments" section. Accordingly, this Office Action is made **FINAL**.

Priority

2. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 and 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention that is also disclosed in the prior application (the parent or original non-provisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35

U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed applications, Application Nos: 10/076,555, 09/217,471, 60/068,755, 60/080,664, 60/105,234, 09/297,648, 60/072,910, 60/075,954, 60/080,114, 60/080,515, 60/105,877, 60/080,666, 09/313,292, 60/085,426, 60/085,537, 60/085,696, 09/854,124, 09/400,947, 60/101,900, 09/404,706, 60/102,180, 60/102,161, 60/102,380, 60/103,815, 60/105,877, 10/629,771, 09/611,527, 60/142, 311, 60/142,310, 09/803,719, 60/188,609, 10/609,021, 09/819,150, 60/192,853, 10/615,618, 09/932,076, 60/226,326, 10/012,697, 60/254,648, and 60/275,688, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The sequence disclosures of prior-filed Application Nos: 10/076,555, 09/297,648, 09/313,292, 09/854,124, 09/404,706, 10/629,771, 09/803,719, 10/609,021, 10/615,618, 10/012,697, and 60/532,830 are described in Table 161 on pages 63-64 of the instant application's specification. According to this table, only Provisional Application 60/532,830 discloses the instant SEQ ID NO: 23702, and as a result, none of the other prior-filed applications provide adequate support for the method of the instant claims. Thus, the effective filing date of the instant application is the filing date of Provisional Application 60/532,830 (**December 23, 2003**). This filing date has been used for prior art purposes.

Claim Objections

3. Claim 9 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the

claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 9 is drawn to the method of claim 7, wherein the gene product is a nucleic acid. However, claim 7 already requires the gene product to be a nucleic acid (see lines 3-4), and therefore, claim 9 fails to further limit the subject matter of claim 7.

Claim Rejections - 35 USC § 112, 2nd paragraph

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 36 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 36 is indefinite, because there is insufficient antecedent basis for the limitation "the patient sample", which is recited in line 2 of the claim. There is sufficient antecedent basis for "the test sample" (see claim 7).

Claim Rejections - 35 USC § 112, 1st paragraph (Enablement)

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7, 9, 11-13, 30-32, and 34-37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that

was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The Nature of the Invention

The instant claims are drawn to methods of detecting cancerous cells and assessing a human subject's risk of having cancer based on an increase in the expression level of a specific gene product (SEQ ID NO: 23702) relative to normal cells. The invention is classified in the unpredictable arts of chemistry and biology.

The Breadth of the Claims

Claims 7, 9, and 11-13 are broadly drawn to methods of detecting breast cancer cells, colon cancer cells, or prostate cancer cells in a test sample obtained from *any* human subject (*i.e.* a human subject from any ethnic population) based solely on the observation of *any* level of over-expression of SEQ ID NO: 23702. Claims 30-32, 34, and 35 are broadly drawn to methods of assessing *any* human subject's risk of having breast cancer, prostate cancer, or colon cancer based solely on an observed increase in the expression level of SEQ ID NO: 23702, a nucleic

acid at least 95% identical to SEQ ID NO: 23702, or a nucleic acid at least 98% identical to SEQ ID: 23702. Claims 36 and 37 are drawn to the methods of claims 7 and 30, respectively, further comprising measuring the expression level of at least one known molecular marker gene in the sample. SEQ ID NO: 23702 is 542 nucleotides in length. There are hundreds of thousands of different nucleic acids having at least 95% identity or 98% identity to SEQ ID NO: 23702, and each of these different polynucleotides may possess different functional properties.

Guidance in the Specification and Working Examples

The specification teaches that the observation of an increase in the expression level SEQ ID NO: 23702 is sufficient for detecting any cancerous cell in any organism or diagnosing any type of cancer in any organism (see pages 3-5), but only provides specific information regarding the relationship between SEQ ID NO: 23702 and cancer in Working Example 105 (see pages 885-898). In this example, normal and cancerous tissues were collected from human subjects known to have breast cancer, colon cancer, or prostate cancer, and RNA was isolated. cDNA probes were then prepared from this RNA and hybridized to arrays of probes (see pages 885-886). The resulting data are presented in Tables 159 and 160 (see pages 894-907).

Table 159 contains the results relevant to the claimed SEQ ID NO: 23702 (see page 897, columns 1-8 of the table). When cDNA from breast cancer patients was hybridized to the array, 17.39-26.09% of the patients showed an increased level of expression of SEQ ID NO: 23702. The number of breast cancer patients studied ranged from 18-23 individuals. In colon cancer patients, the percentage of patients showing increased expression of SEQ ID NO: 23702 ranged from 12% (19 patient samples were studied) to 63.16% (76 patient samples were studied). In

prostate cancer patients, 0.98 – 3.09% of the patients studied showed an increase in the expression level of SEQ ID NO: 23702. Here, the number of patients studied ranged from 64 individuals (1.56% showed increased expression) to 102 individuals (0.98 – 1.96% showed increased expression).

However, regarding claims 7, 9, 11-13, and 36, the specification does not teach in Example 105 or elsewhere that breast cancer, colon cancer, or prostate cancer cells can be detected based solely on the observation of any increase in the expression level of SEQ ID NO: 23702. In the above example, the expression level of SEQ ID NO: 23702 was only measured in cancer patients and does not appear to have been compared to the expression levels measured in cancer-free subjects. Also, the specification does not teach that *any* level of over-expression of SEQ ID NO: 23702 can be used to identify breast cancer cells, prostate cancer cells, or colon cancer cells and provides no discussion as to what level of over-expression must be observed to reliably identify a cell as a cancerous cell. Furthermore, the specification contains no discussion of ethnic populations in which the expression level of SEQ ID NO: 23702 can be used to detect breast cancer cells, colon cancer cells, or prostate cancer cells. Finally, there is no discussion in the specification regarding the low number of positive results observed in Example 105 or the high degree of variability within said positive results.

Similarly, regarding claims 30-32 and 34-37, the specification does not teach assessing an individual's risk of having breast cancer, prostate cancer, or colon cancer based solely on the expression level of SEQ ID NO: 23702. As discussed above, Example 105 only teaches measuring the expression level of SEQ ID NO: 23702 in human subjects with known to have cancer and does not demonstrate that the method can be used to reliably assess cancer risk in

patients or test samples with unknown disease status. In particular, the specification and working examples fail to compare the expression levels of SEQ ID NO: 23702 observed in cancer patients with the expression levels observed in cancer-free individuals, and as a result, it is not clear whether the observed over-expression of SEQ ID NO: 23702 in a small number of cancer patients is associated with cancer. The specification also contains no discussion of ethnic populations in which the expression level of SEQ ID NO: 23702 can be used to assess breast cancer, colon cancer, or prostate cancer risk. Furthermore, the specification does not demonstrate a relationship between the expression level of any of the thousands of variants of SEQ ID NO: 23702 encompassed by the claims and even one type of cancer. The specification does not describe the identity or functional properties of SEQ ID NO: 23702 or variants having 95% or 98% identity thereto. For example, the specification does not describe regions of the resulting protein that are important for function, the function of the protein encoded by a polynucleotide comprising SEQ ID NO: 23702 in the cell, how an alteration in the function of such a protein may be associated with cancer, *etc*. Finally, there is no discussion in the specification regarding the low number of positive results observed in Example 105 or the high degree of variability within said positive results.

State of the Prior Art and Unpredictability

The art does not teach detecting breast cancer cells, prostate cancer cells, or colon cancer cells in a sample or assessing a human subject's risk of having breast cancer, colon cancer, or prostate cancer based on an observed increase in the expression level of SEQ ID NO: 23702. However, the art teaches that, in general, it is entirely unpredictable whether or not the

expression level of a particular gene can be used to detect cancerous cells or assess a subject's risk of having cancer. For example, Russo et al. (Oncogene (2003) 22: 6497-6507; cited previously) teaches that microarray-based gene expression studies are useful for rapidly assessing differential expression between cancerous and normal cells (see abstract and page 6497, column 2 – page 6498, column 1). However, Russo also teaches that different cancers showed differential expression of different genes (see pages 6498 – 6501, where Russo reviews the results of microarray-based expression profiling studies in prostate, oral, breast, and ovarian cancers), thereby demonstrating that the expression level of a single gene is unlikely to function in a diagnostic capacity for any type of cancer. Furthermore, Russo teaches that gene expression results can be unpredictable stating, "False microarray data can be generated from degraded mRNA (page 6503, column 2)." Russo also stated that unpredictability often results from the fact that most human tissue samples used for expression analysis are a mixture of different cells (see page 6503, column 2).

The teachings of Srinivas et al. (The Lancet (2001) 2: 698-704; cited previously) further support the conclusion that the claimed methods are highly unpredictable. Srinivas reviewed methods of cancer diagnosis and prognosis based on microsatellite instability, hypermethylation, single nucleotide polymorphisms, gene expression profiling, and proteomics (see abstract). Regarding the use of biomarkers such as differentially expressed genes for diagnostic purposes, Srinivas states, "The initial phase of biomarker discovery used to focus on single-marker-based approaches but, given the complexity of the carcinogenesis process, it would be difficult to correlate sufficiently any single biomarker to a specific cancer (page 699, column 1)."

The teachings of Reinholz et al. (Clinical Cancer Research (2005) 11(10): 3722-3732; cited previously) provide further evidence of the level of unpredictability inherent in the claimed methods. Reinholz measured the ability of five markers, alone and in several different combinations, to accurately detect a specific type of cancer (breast cancer) in human subjects using RT-PCR to detect differential gene expression (see abstract). The resulting data show significant differences in specificity and sensitivity between the five markers (see Table 4 on page 3729), thus illustrating the unpredictable nature of reliably and reproducibly detecting even a single type of cancer in a human subject based on the observed expression level of a single gene. Reinholz specifically commented on the limitations of using a single marker for cancer detection stating, "Although *mammaglobin* is a promising tumor marker, it is not universally expressed in all breast cancers. Our results showed that ~20% of invasive breast cancer patients did not have detectable levels of *mammaglobin*. Therefore, we evaluated the utility of adding *B305D-C, B726P, GABA* A_π, or *CK-19* to the analysis of *mammaglobin* to discriminate between patients with benign and invasive breast cancer breast biopsies. Our results showed that combining *mammaglobin* with *B305D-C* improved both sensitivity and specificity (page 3730, column 2)."

Furthermore, the disclosure of the instant application supports the conclusion that the claimed methods are highly unpredictable. As discussed above, Table 159 demonstrates that number of patients showing a statistically significant increase in expression of SEQ ID NO: 23702 varied widely between and within the cancer types tested. For example, in colon cancer patients, the percentage of patients showing increased expression of SEQ ID NO: 23702 ranged from 12% (19 patient samples were studied) to 63.16% (76 patient samples were studied). Also,

although the number of breast cancer patients showing increased expression levels of SEQ ID NO: 23702 did not show this extent of intra-cancer variation, the results differed markedly when compared to the colon and prostate cancer patients. These results clearly demonstrate the level of unpredictability present in the claimed methods.

Finally, the variability in the claimed methods observed with SEQ ID NO: 23702 would necessarily extend to polynucleotides having 95% identity or 98% identity to SEQ ID NO: 23702. As discussed above, the genus of nucleic acids having 95% or 98% identity to SEQ ID NO: 23702 is very large and each of the different members will inherently possess different functional properties. Also, as discussed above, the specification provides only minimal information regarding SEQ ID NO: 23702, and most importantly, provides absolutely no discussion regarding regions of this nucleic acid where a mutation is likely to result in a protein having altered transcriptional or translational properties, altered functional properties, *etc.* As a result, it is entirely unpredictable as to whether measuring the expression level of a variant of SEQ ID NO: 23702 can be used to detect cancerous cells or to assess a human subject's risk of having cancer. Likewise, since gene expression is known to vary between different ethnic groups, it is also highly unpredictable as to whether any observed correlation between the expression level of SEQ ID NO: 23702 and cancer could be used in any other population for detection or risk assessment purposes.

Furthermore, the art is replete with evidence that gene association studies are typically wrong. In fact, Lucentini et al. (The Scientist (2004) Vol. 18; cited previously) titled his article "Gene Association Studies Typically Wrong" and stated, "Two recent studies found that typically, when a finding is first published linking a given gene with a complex disease, there is

only roughly a one-third chance that studies will reliably confirm the finding (see page 2 of printout)." This is consistent with the teachings of Wei (BMC Genomics, 2004; cited previously) stating, "Microarray experiments are often performed with a small number of biological replicates, resulting in low statistical power for detecting differentially expressed genes and concomitant high false positive rates (abstract)."

These teachings in the art suggest that gene association studies are highly unpredictable and require extensive validation. Therefore, the observed over-expression of SEQ ID NO: 23702 at the mRNA level in a low percentage of cancer patients in a small sample from an unspecified population(s) cannot be extrapolated to any ethnic population or variants of SEQ ID NO: 23702 without conducting an extensive amount of non-routine experimentation. Also, given the small sample size and low percentage of positive results presented in the only working example, the ability of SEQ ID NO: 23702 to be used reliably in the claimed methods of cancerous cell detection or cancer risk assessment is highly unpredictable.

Quantity of Experimentation

The quantity of experimentation required in this case is immense, because it would require significant study and experimentation including trials with hundreds of patients to determine that increased expression of SEQ ID NO: 23702 is capable of reliably functioning to detect even one type of cancer cells or to assess the risk that human subjects from a single ethnic population have one of the claimed cancers. The amount of experimentation required in either of the above cases would be an inventive, unpredictable and difficult undertaking in itself, requiring years of inventive effort, with no guarantee of success at the conclusion. Furthermore, each of

the different cancers (breast cancer, colon cancer, prostate cancer), each different variant of SEQ ID NO: 23702, and each different ethnic population would require the same extensive trial-and-error type experimentation in order to determine its ability to be used to practice the claimed methods, since the results obtained for each cancer, variant, and human population would not necessarily extend to any of the other cancers, variants, or human populations encompassed by the claims. One would also have to determine the minimum level of over-expression that must be observed in order to reliably detect breast cancer, colon cancer, or prostate cancer cells based on an increase in the expression level of SEQ ID NO: 23702.

The teachings in the pre- and post-filing art support this conclusion regarding the quantity of experimentation required to practice the claimed methods. For example, Feng et al. (Critical Reviews in Clinical Laboratory Sciences (2006) 43(5-6): 497-560; cited previously) teaches that although discovery of promising biomarkers occurs with much less experimental effort than previously, validation of clinical utility remains slow and difficult (page 537, last paragraph). Feng stated, "Biomarker discovery may require only a few weeks and a small number of patient samples, whereas its validation may require thousands of samples from multi-center trials (page 537, last paragraph)." In addition, Feng teaches that detection of a differentially expressed gene does not always correlate with an increased level of protein product (page 538, paragraph), thereby illustrating that upon further experimentation, an initially promising biomarker may be eliminated as a useful diagnostic agent upon further testing. The teachings of Mitas et al. (International Journal of Cancer (2001) 93: 162-171; cited previously) also illustrate the fact that validation of differentially expressed nucleic acids as useful diagnostic markers for even one type of cancer in human subjects requires extensive experimentation with no guarantee of

success. Mitas analyzed the expression level of 12 cancer-associated genes by RT-PCR in tissue samples obtained from breast cancer patients (see abstract). Mitas reported that only half of the tested genes accurately functioned as breast cancer indicators in a specific type of breast cancer – metastatic cancer (see abstract and page 166). As added evidence of the quantity of experimentation required for validating a single gene's predictive capabilities in even one cancer type, Mitas further taught that one of the tested genes, VEGF, although not of diagnostic utility for metastatic breast cancer, could be useful in detecting primary breast cancer (page 169, column 1). Thus, Mitas teaches the same marker may not function as an accurate diagnostic agent for all cancers and further that initially promising genes may not prove to be useful markers upon further analysis. Finally, Srinivas summarizes the extensive effort required to establish the diagnostic value of even a single biomarker in a single cancer in human subject. Srinivas states at pages 702-703:

> The sensitivity, specificity, and predictive value of biomarkers have to be determined through use of body fluids, paired tumours, and surrounding tissue from a wide variety of cancers before they can be used in populations. Many samples from individuals with known characteristics should be processed, to minimize the problems of confounding and to avoid spurious associations. Before field-testing, it should be established that the biomarker is truly in the path of pathogenesis and not merely the result of an adaptive response. Case-control studies on stored samples should be used to test the efficiency of the biomarkers. Although the emerging technologies show great promise, care must be taken to define and establish references or baseline profiles from normal tissue, cells, or body fluids. Extensive animal studies may help refine human testing before screening. The biomarker assay should be reproducible to avoid false-positive and false-negative results and also to provide a substantial lead-time before clinical diagnosis.

Wei et al. (BMC Genomics (2004) 5: 87-96; cited previously) teaches that the gene expression studies conducted using larger sample sizes with more replicates have much better statistical power and relevance compared to studies using small sample sizes with few replicates (see page 2, col. 1 and page 8). So, the quantity of experimentation factor supports the

conclusion that a large quantity of experimentation, with the use of many hundreds, perhaps even thousands, of subject samples would be necessary to demonstrate an association between the over-expression of SEQ ID NO: 23702 and a single type of cancer in a particular ethnic population. These large sample sizes would be required for each different type of cancer, each different variant of SEQ ID NO: 23702, and each different ethnic population. The ordinary artisan would also need to determine what level of over-expression is sufficient for reliable detection of breast cancer cells, colon cancer cells, or prostate cancer cells. The minimum expression level required for reliable detection may differ for different cancers, different variants of SEQ ID NO: 23702, and different ethnic populations, and therefore, would require independent determination.

In short, in order to use the claimed methods, the ordinary artisan would be required to perform extensive case-control experimentation in an effort determine that any observed increase in the level of expression of SEQ ID NO: 23702 can be used to reliably detect breast cancer cells, colon cancer cells, or prostate cancer cells in a sample obtained from a human subject from a particular ethnic population. An ordinary artisan would also have to perform extensive case-control experimentation in an effort to determine that a particular level of over-expression of SEQ ID NO: 23702 or a variant at least 95% or at least 98% identical thereto can be used to reliably assess the risk of a human subject from any ethnic population of having breast cancer, colon cancer, or prostate cancer. Even if such experimentation were to be performed, one might find that there is no significant association between over-expression of SEQ ID NO: 23702 or a variant thereof and the particular cancer in the particular ethnic population. Each set of experiments would be essentially independent from the others, and success in one set of

experiments would not necessarily be predictive of success in another set of experiments. Furthermore, each set of experiments would be conducted with no guarantee of success. This is a very large amount of experimentation.

The Level of skill in the art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, the instant claims are broadly drawn to methods of detecting a cancerous breast, colon, or prostate cell in a human subject and assessing a human subject's risk of having breast cancer, colon cancer, or prostate cancer based solely on an observed increase in the expression level of SEQ ID NO: 23702 or a variant having at least 95% or at least 98% identity to SEQ ID NO: 23702. Despite the breadth of the claims, the specification only teaches detection of cancerous breast, colon, and prostate cells from human subjects known to have one of these types of cancer, and even these limited results show a high degree of variability (*i.e.* unpredictability) and a low rate of success. Also, the specification does not demonstrate the ability of any of the claimed variants of SEQ ID NO: 23702 to be used in the recited methods. Furthermore, the specification provides no guidance regarding methods of validation or how to overcome the art-recognized problems of reliable detection or risk assessment based on the expression level of a single gene. Thus, given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, balanced only against the high skill level in the art, it is the position of the

examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Rejections - 35 USC § 112, 1st paragraph (Written Description)

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7, 9, 11-13, 30-32, and 34-37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The central inquiry when considering written description is whether an ordinary artisan would reasonably conclude that Applicant was in possession of the claimed invention at the time of filing (see MPEP 2163 and *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1566-67, 43 USPQ2d 1398, 1404-05 (Fed. Cir. 1997); *Hyatt v. Boone*, 146 F.3d 1348, 1354, 47 USPQ2d 1128, 1132 (Fed. Cir. 1998)).

According to Revision I of the Written Description Training Materials (posted 4/11/08 at http://www.uspto.gov/web/menu/written/pdf), the following factors should be considered, when evaluating a claim for compliance with the written description requirement: (a) actual reduction to practice, (b) disclosure of drawings or structural chemical formulas (c) sufficient relevant

identifying characteristics (d) method of making the claimed invention, (e) level of skill and knowledge in the art, and (f) predictability in the art (see page 1 of the Training Materials).

Claims 7, 9, and 11-13 are drawn to methods of detecting a cancerous breast, colon, or prostate cell in a test sample obtained from any human subject (*i.e.* a human subject from any ethnic population) based solely on the observation of any level of increased expression of SEQ ID NO: 23702. Claims 30-32, 34, and 35 are drawn to methods of assessing any human subject's risk of having breast cancer, prostate cancer, or colon cancer based solely on an observed increase in the expression level of a nucleic acid at least 95% identical to SEQ ID NO: 23702, a nucleic acid at least 98% identical to SEQ ID: 23702, and SEQ ID NO: 23702, respectively. SEQ ID NO: 23702 is 542 nucleotides in length. Claims 36 and 37 are drawn to the methods of claims 7 and 30, respectively, wherein the methods further comprise measuring the expression level of at least one known molecular marker gene in the sample. There are hundreds of thousands of different nucleic acids having at least 95% identity or 98% identity to SEQ ID NO: 23702, each of which may possess very different functional properties. It is a critical feature of the claimed methods that an observed increase in the expression level of SEQ ID NO: 23702 or variants having 95% or 98% identity thereto is associated with breast cancer, prostate cancer, or colon cancer.

The specification teaches that the observation of an increase in the expression level SEQ ID NO: 23702 is sufficient for detecting any cancerous cell in any organism or diagnosing any type of cancer in any organism (see pages 3-5), but only provides specific information regarding the relationship between SEQ ID NO: 23702 and cancer in Working Example 105 (see pages 885-898). In this example, normal and cancerous tissues were collected from human subjects

whose known to have breast cancer, colon cancer, or prostate cancer, and RNA was isolated. cDNA probes were then prepared from this RNA and hybridized to arrays of probes (see pages 885-886). The resulting data are presented in Tables 159 and 160 (see pages 894-907).

Table 159 contains the results relevant to the claimed SEQ ID NO: 23702 (see page 897, columns 1-8 of the table). When cDNA from breast cancer patients was hybridized to the array, 17.39-26.09% of the patients showed an increased level of expression of SEQ ID NO: 23702. The number of breast cancer patients studied ranged from 18-23 individuals. In colon cancer patients, the percentage of patients showing increased expression of SEQ ID NO: 23702 ranged from 12% (19 patient samples were studied) to 63.16% (76 patient samples were studied). In prostate cancer patients, 0.98 – 3.09% of the patients studied showed an increase in the expression level of SEQ ID NO: 23702. Here, the number of patients studied ranged from 64 individuals (1.56% showed increased expression) to 102 individuals (0.98 – 1.96% showed increased expression).

However, regarding claims 7, 9, 11-13, and 36, the specification does not teach in the working examples or elsewhere that breast cancer, colon cancer, or prostate cancer cells can be detected based solely on the observation of an increase in the expression level of SEQ ID NO: 23702. In the above example, the expression levels of SEQ ID NO: 23702 were only measured in cancer patients and do not appear to have been compared to the expression levels measured in cancer-free subjects. Also, the specification does not teach that *any* level of over-expression of SEQ ID NO: 23702 can be used to identify breast cancer cells, prostate cancer cells, or colon cancer cells and provides no discussion regarding what level of over-expression must be observed to reliably identify a cell as a cancerous cell. The specification also contains no

discussion of ethnic populations in which the expression level of SEQ ID NO: 23702 can be used to detect breast cancer cells, colon cancer cells, or prostate cancer cells. Finally, there is no discussion in the specification regarding the low number of positive results observed in Example 105 or the high degree of variability within said positive results.

Similarly, regarding claims 30-32 and 34-37, the specification does not teach assessing an individual's risk of having breast cancer, prostate cancer, or colon cancer based solely on the expression level of SEQ ID NO: 23702. As discussed above, the working example only teaches measuring the expression level of SEQ ID NO: 23702 in human subjects known to have cancer and does not demonstrate that the method can be used to reliably assess cancer risk in patients or test samples with unknown cancer status. In particular, the specification and working examples fail to compare the expression levels of SEQ ID NO: 23702 observed in patients known to have cancer with the expression levels of SEQ ID NO: 23702 observed in cancer-free individuals, and therefore, it is not clear whether the observed increase in expression of SEQ ID NO: 23702 in a small number of cancer patients is associated with cancer. The specification also contains no discussion of ethnic populations in which the expression level of SEQ ID NO: 23702 can be used to assess breast cancer, colon cancer, or prostate cancer risk. Furthermore, the specification does not demonstrate a relationship between the expression level of any of the thousands of variants of SEQ ID NO: 23702 encompassed by the claims and cancer. The specification does not describe the identity or functional properties of SEQ ID NO: 23702 or variants having 95% or 98% identity thereto. For example, the specification does not describe regions of the resulting protein that are important for function, the function of the protein encoded by a polynucleotide comprising SEQ ID NO: 23702 in the cell, how an alteration in the function of such a protein

may be associated with cancer, *etc*. Finally, there is no discussion in the specification regarding the low number of positive results observed in Example 105 or the high degree of variability within said positive results.

As a result, the specification does not adequately describe methods of detecting breast cancer cells, prostate cancer cells, or colon cancer cells in any ethnic population based on any level of over-expression of SEQ ID NO: 23702. The specification also fails to adequately describe methods of assessing the risk of a human subject from any ethnic population for having breast cancer, colon cancer, or prostate cancer based on an observed increase in the expression level of SEQ ID NO: 23702 or variants having 95% or 98% identity thereto. As discussed above, the only relevant working example presented in the specification does not demonstrate a statistically significant association between the expression level of SEQ ID NO: 23702 and breast cancer, colon cancer, or prostate cancer. In other words, the specification does not contain an actual reduction to practice of the claimed methods. The specification also fails to teach the relevant identifying characteristics required to satisfy the written description requirement, since it contains no discussion the following: (1) minimum levels of over-expression of SEQ ID NO: 23702 required to reliably detect breast cancer cells, colon cancer cells, or prostate cancer cells, (2) whether the expression level of SEQ ID NO: 23702 can be used to detect cancerous cells or assess cancer risk in different ethnic populations, and (3) which variants of SEQ ID NO: 23702 are expected to be useful in detecting cancerous cells or assessing cancer risk. As discussed above, there is a high level of unpredictability in methods of cancer screening and detection based on the expression level of a single gene, and as a result, the level of skill in the art required to practice the invention is high. Also, as discussed above, the claimed methods were unknown

in the art at the time of filing. Therefore, it must be concluded that Applicant was not in possession of the claimed invention at the time of filing.

Response to Arguments

7. Applicant's arguments filed on June 23, 2009 regarding the rejections made under 35 U.S.C. 112, first paragraph (enablement and written description) have been fully considered, but they were not persuasive. In view of the addition of claims 36 and 37, these rejections currently apply to claims 7, 9, 11-13, 30-32, and 34-37.

Regarding the rejection of claims 7, 9, 11-13, 30-32, and 34-37, Applicant first argues that the specification provides more than enough guidance for the ordinary artisan to practice the claimed methods without undue experimentation (pages 5-7). In particular, Applicant argues that the proper standard for assessing undue experimentation is not whether or not the experimentation is complex or large in quantity, but rather, whether or not the ordinary artisan typically engages in such experimentation (pages 5-6). Applicant argues that the ordinary artisan would only need to conduct routine experimentation in combination with the guidance presented in the specification to practice the claimed methods (pages 5-6). Applicant further argues that the claimed methods are only drawn to methods of assessing risk and not methods of detecting or diagnosis as implied in the rejection, and that the disclosure provides more than enough guidance for conducting the claimed methods (pages 6-7). Finally, Applicant argues that the variability in the data presented in working example 105 is irrelevant to the question of enablement, since the claimed methods are drawn assessing risk rather than detection or diagnosis (page 7). Applicant

argues, therefore, that demonstrating that some percentage of cancer patients shows increased levels of SEQ ID NO: 23702 compared to normal tissues is sufficient (page 7).

Applicant's arguments have been fully considered, but they were not persuasive. As discussed previously, although the ordinary artisan could conduct the experimentation required using standard molecular biological techniques (*i.e.* measuring the expression level of SEQ ID NO: 23702 and its variants in a plurality of different samples obtained from different patients and performing statistical analysis to determine if a significant correlation exists between the observed expression level and cancer), the amount of experimentation required to reasonably enable the claimed methods is considered undue. In other words, although the ordinary artisan would utilize known methods in molecular biology methods to conduct the necessary experimentation, the amount of experimentation and the analysis of the results obtained during the experimentation would be unpredictable and non-routine. Specifically, the ordinary artisan would have to perform extensive amounts of trial-and-error experimentation, with essentially no guidance from the specification, in order to determine the following: (1) minimum increases in the expression level of SEQ ID NO: 23702 useful for reliably assessing the risk of breast cancer, colon cancer, and prostate cancer and for assessing the risk that a sample obtained from a human subject contains a cancerous breast, colon, or prostate cell, (2) ethnic populations in which the expression of SEQ ID NO: 23702 can be used to reliably assess the risk that test samples obtained from these subjects contains breast cancer cells, colon cancer cells, or prostate cancer cells or assess the subject's risk of having one of the aforementioned cancers, and (3) which variants of SEQ ID NO: 23702 are capable of functioning as reliable indicators of cancerous cells or indicators of cancer.

The ordinary artisan would also have to demonstrate that over-expression of SEQ ID NO: 23702 only occurs in cancerous breast, colon, or prostate tissue from cancer patients and not in breast, colon, or prostate tissue from cancer-free individuals. As discussed above, working example 105 does not include a comparison to a cancer-free, normal control. In other words, the normal breast, colon, and prostate cancer samples used in the example were obtained from cancer patients. As a result, the ordinary artisan could not determine from the data presented in Example 105 whether SEQ ID NO: 23702 is capable of being used to assess a human subject's risk of having a cancer or the likelihood that a test sample contains a cancerous breast, colon, or prostate cell. At most, the ordinary artisan would conclude from the data presented in working example 105 that, in a small sample cancer patients, SEQ ID NO: 23702 is over-expressed in some of the tested cancerous breast, colon, or prostate tissues relative to normal breast, colon, or prostate tissues obtained from the same patients. The high levels of variability in the results obtained from patients known to have breast cancer, colon cancer, or prostate cancer suggests that the claimed methods are associated with a high degree of variability and unpredictability. For example, since only 1-3% of patients known to have prostate cancer showed an increase in the expression level of SEQ ID NO: 23702, it is unclear how the ordinary artisan could reasonably assess a subject's risk of having prostate cancer using the expression level of SEQ ID NO: 23702.

Regarding the issue of undue experimentation, section 2164.06 of the MPEP provides the following guidance, "The quantity of experimentation needed to be performed by one skilled in the art is only one factor involved in determining whether 'undue experimentation' is required to make and use the invention. '[A]n extended period of experimentation may not be undue if the

skilled artisan is given sufficient direction or guidance.' *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977)." In this case, as discussed above, the specification provides only minimal guidance, and this lack of guidance combined with the inherent unpredictability in the claimed methods requires the ordinary artisan to perform a large quantity of experimentation with little or no starting point and with no guarantee of success. This constitutes undue experimentation.

It is further noted that although the claimed methods are directed to risk assessment rather than diagnosis or detection of cancer, they still require a correlation between the expression level of SEQ ID NO: 23702 or a variant thereof and colon, breast, or prostate cancer. In other words, a cell contained in a test sample cannot be positively identified as a cancerous cell and risk cannot be assessed unless there is a significant correlation between cancer and the expression level of the particular gene. In this case, as discussed above, neither the only relevant working example (Example 105) nor the art teaches that there is a correlation between the expression level of SEQ ID NO: 23702 and breast cancer, prostate cancer, or colon cancer. Also, neither the specification nor the art teaches a correlation between variants having at least 95% or at least 98% identity to SEQ ID NO: 23702 and the cancers recited in the claims. As discussed above, Example 105 only indicates that, in a small sample cancer patients, SEQ ID NO: 23702 is over-expressed in some of the tested cancerous breast, colon, or prostate tissues relative to normal breast, colon, or prostate tissues obtained from the same patients. Since the expression level SEQ ID NO: 23702 in breast, colon, and prostate tissues obtained from normal, cancer-free individuals was not determined, it cannot be concluded from the data presented in Example 105

that the required correlation between the expression level of SEQ ID NO: 23702 and breast cancer, colon cancer, and prostate cancer exists.

Finally, Applicant's argument that the variability in the data presented in Example 105 is irrelevant to the question of enablement (see page 7) was unpersuasive. Although Applicant is correct that the claimed methods are directed to risk assessment rather than cancer diagnosis or detection, the variability in the results presented in Example 105 suggests that even methods of risk assessment could only be reliably performed after an conducting an extensive amount of additional non-routine experimentation, in particular, to account for the fact that the results obtained in Example 105 do not include results obtained from normal, cancer-free individuals.

Since Applicant's arguments were not found persuasive, the rejection has been maintained with modifications to account for the claim amendments.

Regarding the rejection of claims 7, 9, 11-13, 30-32, and 34-37 under 35 U.S.C. 112, first paragraph (written description), Applicant first argues that the claims are directed to methods of assessing risk rather than methods of cancer detection or diagnosis, and therefore, the rejection inappropriately requires a much more extensive disclosure than is necessary to demonstrate that the Applicant was in possession of the claimed invention (see pages 8-9). Applicant also argues that the specification contains a reduction to practice of the claimed methods of risk assessment in Example 105 (page 9). Applicant further argues that the original disclosure satisfies the requirement to set forth the relevant identifying characteristics of the claimed invention in at least Example 105 (page 10).

Applicant's arguments were not persuasive, because the claimed methods of risk assessment have not been adequately described in the original disclosure. There is no actual

reduction to practice of risk assessment and insufficient description of the relevant identifying characteristics, since the only working example utilizes samples obtained from patients whose cancer status is known. As a result, Example 105 functions at most as a proof of principle, and not an actual reduction to practice, since there is no demonstration that the expression level of the claimed nucleic acid can be used to assess samples obtained from patients of unknown disease status. Also, the specification fails to teach the relevant identifying characteristics necessary for practice of the invention, because the data presented in the only relevant working example does not establish that a correlation exists between the expression level of the claimed nucleic acid and breast cancer, colon cancer, and prostate cancer.

Since Applicant's arguments were not found persuasive, the rejection has been maintained with modifications to account for the claim amendments.

Conclusion

8. No claims are currently allowable. The claimed methods are free of the art, but they have been rejected for other reasons, specifically failure to comply with the written description and enablement requirements of 35 U.S.C. 112, first paragraph.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANGELA BERTAGNA whose telephone number is (571)272-8291. The examiner can normally be reached on M-F, 7:30 - 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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